REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim 4 is cancelled without prejudice.

The objection to claim 4 as being in improper dependent form is thus deemed to be overcome.

Claim 1 has been amended to replace the term "any drug" with the phrase "a compound of formula I", as kindly suggested by the Examiner.

Thus, the rejection of claims 1-22 under 35 USC 112, first paragraph, is deemed to be overcome.

Furthermore, the rejection of claims 1-22 under 35 USC 112, second paragraph, is deemed to be overcome.

Claims 1-9, 12, 14-18 and 22 are rejected under 35 USC 102 as being anticipated by EP 0 636 364. This ground of rejection is respectfully traversed.

Claim 1 is directed to an oral pharmaceutical composition containing at least two separate formulations. The cited reference fails to disclose an oral pharmaceutical composition containing at least two separate formulations according to the claimed invention.

EP 0 636 364 relates to an oral pharmaceutical composition comprising a substance belonging to the family of substituted benzhydrylpiperazines and at least one cyclodextrin.

Example 6 describes that cetirizine dihydrochloride and beta cyclodextrine are mixed together in the presence of water to form a complex. Said complex is then further mixed with excipients and then compressed to form an oral composition. EP 0 636 364 thus discloses a single formulation comprising a mixture of the active substance, a cyclodextrin and excipients and thus is different from the claimed oral composition which comprises two separate formulations. Claim 1 (and consequently all dependent claims) is therefore novel over EP 0 636 364.

The instant invention seeks to provide oral compositions with improved taste which comprise palatability improving polyols while avoiding any stability impairment

of the active ingredient by the polyols. See pages 2-4 of the specification. Such a problem is not addressed by EP 0 636 364. Therefore, by reading this document, not only would the person skilled in the art not be aware of such a problem but the person skilled in the art would have no incentive to solve it. In the most unlikely case that a person skilled in the art would try to solve the problem, he would be led away from the solution provided by this invention. Indeed, all examples of EP 0 636 364 relate to oral compositions comprising a single formulation containing a mixture of an active substance, a cyclodextrin and polyols - not to an oral composition comprising two separate formulations having the characteristics defined in claim 1 of the specification. Therefore, claim 1 is inventive with respect to EP 0 636 364.

The compounds according to formula I are orally active and selective histamine H_1-receptor antagonists. They are described in EP 0 058 146. Examples of these compounds include cetirizine, in its dihydrochloride form marketed under the tradename Zyrtec®, the (S) enantiomer thereof, levocetirizine, in its dihydrochloride form marketed under the tradename Xyzal® and efletirizine in its dihydrochloride form.

A serious problem encountered with oral formulations of these active compounds is their taste caused by the bitterness of the active compounds of formula I. This is particularly pronounced in chewable and quickly dissolving preparations.

Several attempts have been made in the prior art to mask the bitterness of active agents in general.

U.S. 5,244,881 for example teaches that inclusion into cyclodextrin can mask the bitter taste of the active agent imipramine or its derivative trimipramine. The inclusion complex is prepared by dissolving imipramine or trimipramine and cyclodextrin in a small amount of water or solvent, carefully mixing the mixture obtained and evaporating the said mixture.

However, masking the taste is not always sufficient to obtain palatable pharmaceutical compositions. Good palatability usually further necessitates addition of polyols to the composition. The term "polyol" includes xylitol, mannitol, sorbitol, dextrose, sucrose, lactose, maltodextrins, alpha cyclodextrins, beta cyclodextrins, gamma cyclodextrins and polysaccharides, but is not limited thereto. Mannitol has proven to be a particularly suitable substance for the improvement of the palatability of preparations

containing active compounds of formula I. Such compositions have, however, an important drawback. Compounds of formula I in the presence of certain polyols, including mannitol, can result in undesired reaction products such as for example those disclosed in EP 0 811 374 Al. This side reaction is increased in presence of water and/or by an increase of temperature. The presence of mannitol and other polyols may thus create a stability problem for compounds of formula I.

Until now, to avoid undesired reaction products, there was no choice but to avoid the presence of these polyols in compositions or to coat active compounds of formula I for example with a cellulose or acrylate polymer prior to formulation.

In the first case, using other excipients like microcrystalline cellulose impairs the taste of the tablets by the fact that microcrystalline cellulose is not entirely soluble in water and therefore can leave a sand-like feeling in the mouth.

In the second case, the thickness of the coating necessary for avoiding interactions between the active compounds of formula I and the polyol(s) impedes rapid liberation of the drug from the pharmaceutical form.

EP 0 811 374 Al teaches that the entire dosage form must be free of reactive alcohols, including polyols. Therefore, palatability improving polyols may not be used in the entire oral composition according to this disclosure. Example 2 of EP 0 811 374, which is stated to demonstrate a preferred embodiment, clearly shows the absence of palatability improving polyols; the only polyol present in this composition is polyethyleneglycol, a high molecular weight polyol (MW 3350) which has a function different from taste masking.

It is the aim of the present invention to overcome this drawback of stability loss in the presence of polyols in a way which is both palatable and avoids disadvantageous changes in product performance.

The problem to be solved by the invention was therefore to improve the taste and palatability of oral compositions containing active compounds of formula I and palatability improving polyols whilst at the same time avoiding any stability impairment and maintaining optimal release kinetics for the active compound.

Taste masking polyols generally are solid and have a molecular weight of less than 3000.

The inventors have found that stability loss caused by interaction of active compounds of formula I and polyols correlates with decreasing molecular weights of the polyols.

Table 1. Molecular weights of some polyols

Polyols	MW
Xylitol	152.15
Mannitol	182.17
Sorbitol	182.17
Dextrose	198.17
Sucrose	342.30
Lactose	342.30
Maltodextrins	from 900.00
Alpha cyclodextrin	972.00
Beta cyclodextrin	1135.00
Gamma cyclodextrin	1297.00
Microcrystalline cellulose	36000

Generally, polyols with a low molecular weight, such as xylitol, mannitol, sorbitol, dextrose or sucrose (see Table 1) are reactive or very reactive and cause a large amount of undesired reaction products. On the other hand, polyols with a high molecular weight, such as cyclodextrins (see Table 1) are very little reactive.

Surprisingly, this correlation between the molecular weight and the reactivity is not true for lactose. Lactose has the same molecular weight as sucrose but shows practically no reactivity with the active compounds of formula I.

Very reactive polyols may therefore be defined as those polyols having a molecular weight of less than 300. Reactive polyols are those having a molecular weight between 300 and 950, with the exception of lactose.

It has further been found by the inventors that even reactive and very reactive polyols do not cause untolerable amounts of undesired reaction products with the active compounds of formula I if the molar ratio between these polyols and the active compound does not exceed 10. If the molar ratio between reactive or very reactive

polyols and the active compound of formula I is not above 5, the percentage of undesired side products is even further minimised.

Based on these findings, the technical problem has been solved according to the present invention by providing a composition prepared from two separate formulations which contains in the first formulation the active compound of formula I and reactive or very reactive polyols only up to a critical level and which contains in the second formulation the polyols necessary to achieve a pleasant taste but no drug compound. Thereby, formation of undesired reaction products is largely eliminated and the unpleasant taste is efficiently reduced or masked.

This solution of the problem is very different from the teaching in EP 0 811 374 Al. This document teaches that the dosage form should be substantially free of reactive alcohols at the time the immediate-release cetirizine component is introduced into the dosage form and thereafter, thus reactive polyols do have to be excluded from the entire composition. The alcohols disclosed in EP 0 811 374 Al perform a function completely different from this invention, namely either as solvents (low molecular weight alcohols such as methanol, ethanol, isopropanol and glycerin) or as high molecular weight compounds (polyethylene glycol) to facilitate release of pseudoephedrine. The low molecular weight alcohols are removed before cetirizine is added to prevent undesired reaction products.

According to the present invention reactive polyols may be present in any amount in the second layer. Indeed, the presence of solid polyols with a molecular weight of less than 3000 in the second formulation according to the invention is needed for palatability improvement which is essential for pharmaceutical compositions which are chewable or quickly dissolving.

In summary, the cited reference fails to disclose or suggest the claimed composition.

Claims 1-8, 12-15, 19-20 and 22 are rejected under 35 USC 102 as being anticipated by Johnson et al. (U.S. 6,627,234). This ground of rejection is respectfully traversed.

U.S. 6,627,234 describes a method of producing active agent coated chewing gum products and relates to delivery issues mainly. The medicament is present within the

coating of a chewing gum composition, and the medicament is added to the gum coating (col. 2, lines 59-66). Gum coatings may contain polyols, and in fact in the examples U.S. 6,627,234 at least a polyol (sorbitol, mannitol, sugar, dextrose, xylitol, etc.) is present within the chewing gum coating, so as to be in the same layer as the active agent.

This is contrary to the claimed invention wherein the first formulation contains the active compound and does not contain polyols having a molecular weight of less than 300.

Therefore, the claims under examination are novel over U.S. 6,627,234.

Accordingly, this ground of rejection is deemed to be overcome.

Claims 1-9, 12, 14-16 and 21-22 are rejected under 35 USC 102 as anticipated by Fekete et al. (U.S. 5,543,155).

This ground of rejection is respectfully traversed.

U.S. 5,543,155 describes a diffusion-osmotic controlled drug-release pharmaceutical composition comprising a two-layer tablet core. The first layer of the tablet contains an active ingredient (drug, medicament), a hydrophilic polymer, filing material (cellulose, starch, lactose, mannitol), binding material and lubricant; the second layer contains a hydrophilic polymer, filing material, binding material and lubricant (claims 11, 14 and 16).

This is contrary to the claimed invention wherein the first formulation contains the active compound and does not contain polyols having a molecular weight of less than 300, so it does not contain mannitol.

Therefore, the claims under examination are novel over U.S. 5,543,155.

Moreover, none of the cited documents are focused on active compounds of formula I of the invention under examination, so the serious problem encountered with oral formulations of these active compounds regarding their taste caused by the bitterness of the active compounds of formula I is never discussed in the documents. The same situation occurs with the issue to overcome the drawback of stability loss in the presence of polyols in a way which is both palatable and avoids disadvantageous changes in product performance.

The problem solved by the invention, i.e. to improve the taste and palatability of oral compositions containing active compounds of formula I and palatability improving

polyols while at the same time avoiding any stability impairment and maintaining optimal release kinetics for the active compound, is never discussed in the cited references. Consequently a person skilled in the art would not read the said references to find a solution to the specific problem of this invention.

Accordingly, this ground of rejection is deemed to be overcome.

Lastly, claims 10-11 are rejected under 35 USC 103 as unpatentable over Fekete et al. (U.S. 5,543,155) in view of Fanara et al. (U.S. 2004/0170690). This ground of rejection is respectfully traversed.

Claim 10 is dependent upon claim 1. Claim 1 is deemed to be novel and not obvious from Fekete et al. for the reasons set forth above. Accordingly, claim 10 is deemed to be patentable over Fekete et al. since Fanara et al. does not remedy the deficiencies of Fekete et al. as applied to claim 1.

Furthermore, please note that the cited US application no. 2004/0170690 is a published patent application of the instant inventors. Therefore the reference is not available under 102(a) but is available under 102(b) as prior art. Under 102(b), the inventors enjoy the "one year grace period" for filing a US patent application. The effective US filing date of the instant invention is the PCT filing date of January 14, 2003. The cited patent publication was published after the effective US filing date of this application (i.e. September 2, 2004). Hence the cited publication is not prior art against this application under 102(b).

The cited patent publication is not a prior art reference under 35 USC 102(e), because 102(e) only applies to publications "by another". In this case, the instant inventors are identical to the inventors of the cited patent publication.

However the cited patent publication is based upon PCT/EP02/06342 which was published in English on January 9, 2003. The parent PCT application was thus published before the filing date of the PCT international application upon which the instant application is based (i.e. January 14, 2003) and is itself prior art, not US application no. 2004/0170690. However the PCT publication date is after the filing date of the EP priority application upon which the instant application is based (i.e. January 15, 2002). Accordingly, if the EP priority application supports the claimed invention under 35 USC 112, it would be possible to remove the published PCT application as prior art.

Submitted herewith is a certified copy of the EP priority application no. 02000871.0 filed January 15, 2002. It is respectfully submitted that the European priority application supports the claimed subject matter under 35 USC 112. Accordingly, it is respectfully submitted that the Fanara et al. cited reference is removed as prior art.

Accordingly, the rejection is deemed to be overcome.

In summary, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Request for Acknowledgement of Foreign Priority

In item 12 of the Office Action on page 1, the Examiner has failed to acknowledge the claim of priority and has failed to acknowledge receipt of all certified copies of the priority documents from the International Bureau. Acknowledgment is respectfully solicited.

Respectfully submitted,

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